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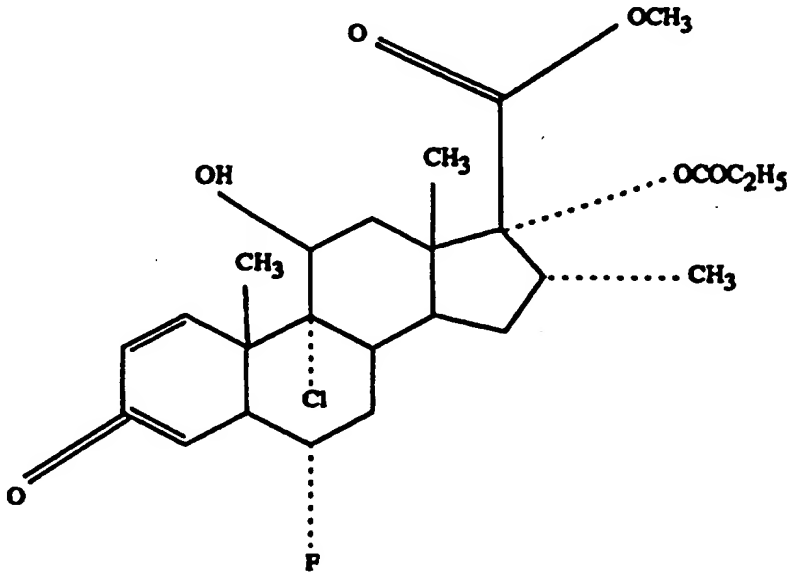
(54) Title: LIPOSOMES CONTAINING A CORTICOSTEROID

(57) Abstract

A pharmaceutical composition comprising, as active ingredient, a compound of formula (I) contained in liposomes or dehydrated liposomes.



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LIPOSOMES CONTAINING A CORTICOSTEROID

The invention relates to pharmaceutical compositions containing a particular corticosteroid as active ingredient, especially for use in the treatment of asthma by inhalation therapy, and a process for the preparation of such pharmaceutical compositions.

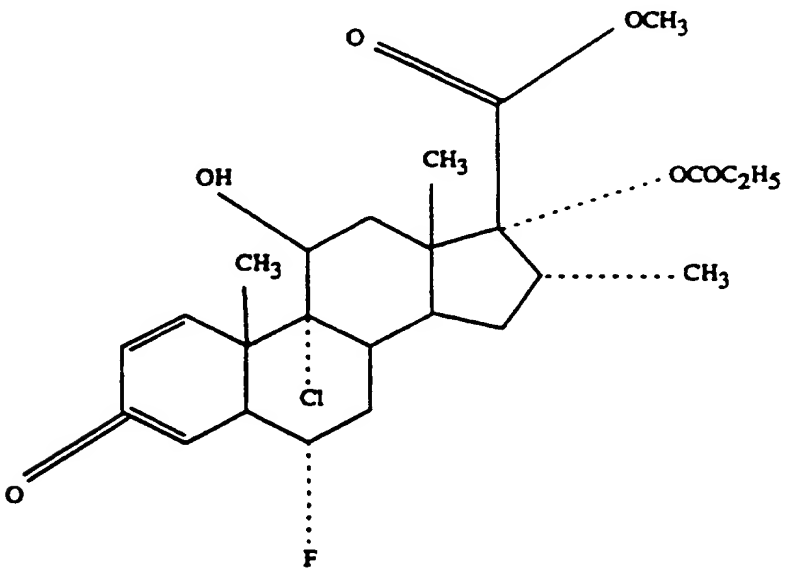
Largely as a result of increasing environmental pollution, obstructive bronchopulmonary diseases such as bronchitis and bronchial asthma have become widespread. Their pathogenesis and severity vary from individual to individual. Extrinsic allergic bronchial asthma, caused by environmental influences (e.g. waste gases, weather inversion layers), and intrinsic bronchial asthma are often characterised by severe attacks with varying respiratory distress. The intensity of coughing and expectoration also vary. Transitional and mixed forms of asthma are frequent and have to be taken into account in therapeutic treatment.

For the treatment of such disorders of differing intensity and genesis, three defined groups f active ingredients with acceptable risk are available, apart from combination formulations. These three groups are β_2-adrenergic agents such as adrenaline, bamethan, clenbuterol, fenoterol, sulbutamol and terbutaline, xanthine derivatives such as theophylline and diprophylline and antichlolinergics containing the atropine derivatives ipatropium bromide and oxitropium bromide. Where therapy with formulations based on these three groups of active ingredients is unsuccessful, the use of certain corticosteroids such as beclomethasone or budesonide, administered orally or by inhalation, is recommended. The only corticosteroid formulations used in existing inhalation therapy have, in addition to the desired antiallergic, antiexudative - anti-inflammatory properties, slight but undersirable systemic side effects arising from absorption of the inhaled corticosteroid. Inhalation therapy using corticosteroids usually has to be carried out over many years, significantly increasing the problem of systemic side effects.

It has now surprisingly been found that methyl 9α-chloro - 6α-fluoro - 11β hydroxy 16α-methyl - 3-oxo - 17α-propionyloxyandrosta-1, 4-diene-17β-carboxylate, previously suggested as an active ingredient for dermatological ointments, creams, gels and foams,

has particularly good antiasthmatic properties when administered entrapped in liposomes. It has also been found that the systemic absorption observed for this compound is surprisingly low.

Accordingly, the present invention provides, in one aspect, a pharmaceutical composition comprising, as active ingredient, a compound of formula I



I

contained in liposomes or dehydrated liposomes.

The compound of formula I, methyl 9α-chloro-6α-fluoro - 11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1, 4-diene-17β-carboxylate, may be prepared as described in British Patent Specification No. 1 578 243. For administration using an inhalation device, the liposomes may be in aqueous suspension or, in dehydrated form, as a dry powder.

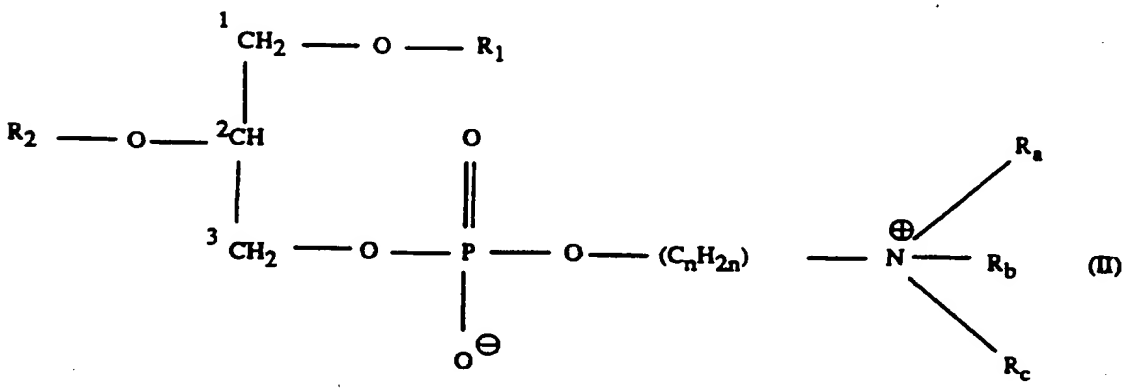
It has been found that liposomes containing the compound of formula I exhibit ready uptake by alveolar macrophages and effective inhibition of eosinophil recruitment in a Brown - Norway rat model of allergen-induced eosinophilia.

Suitable liposomes generally include those in which the lipid component comprises at least one synthetic phospholipid. Examples of synthetic phospholipids are synthetic phosphatidylcholines such as dimyristoyl phosphatidylcholine, dipalmitoyl

phosphatidylcholine, distearoyl phosphatidylcholine, dioleoyl phosphatidylcholine, dilinoleoyl phosphatidylcholine, dilauryloyl phosphatidylcholine, 1-palmitoyl-2-oleoyl phosphatidylcholine, 1-myristoyl-2-palmitoyl phosphatidylcholine and 1-palmitoyl-2-myristoyl phosphatidylcholine, synthetic phosphatidylglycerols such as dilauryloyl phosphatidylglycerol, dimyristoyl phosphatidylglycerol, dipalmitoyl phosphatidylglycerol and dioleoyl phosphatidylglycerol, synthetic phosphatidic acids such as dimyristoyl phosphatidic acid and dipalmitoyl phosphatidic acid, synthetic phosphatidylethanolamines such as dimyristoyl phosphatidylethanolamine and dipalmitoyl phosphatidylethanolamine and synthetic phosphatidylserines such as dimyristoyl phosphatidylserine, dipalmitoyl phosphatidylserine and dioleoyl phosphatidylserine.

Preferably, the lipid component of the liposomes comprises a synthetic phosphatidylcholine such as those hereinbefore described optionally together with a synthetic phosphatidylserine or synthetic phosphatidylglycerol such as those hereinbefore described, the weight ratio of the phosphatidylcholine to the phosphatidylserine or phosphatidylglycerol preferably being from 60:40 to 95:5, especially from 70:30 to 90:10.

In one preferred embodiment, the lipid component of the liposomes comprises a synthetic, substantially pure phospholipid of formula



(II)

wherein R_1 is C_{10}-C_{20} alkanoyl having an even number of carbon atoms, R_2 is C_{10}-C_{20} alkenoyl having an even number of carbon atoms, R_a, R_b and R_c are hydrogen or C_1-C_4 alkyl and n is an integer from two to four.

In a phospholipid of formula II, R_1 as C_{10}-C_{20} alkanoyl having an even number of carbon

atoms is preferably n-dodecanoyl, n-tetradecanoyl, n-hexadecanoyl, n-octadecanoyl or n-eicosanoyl.

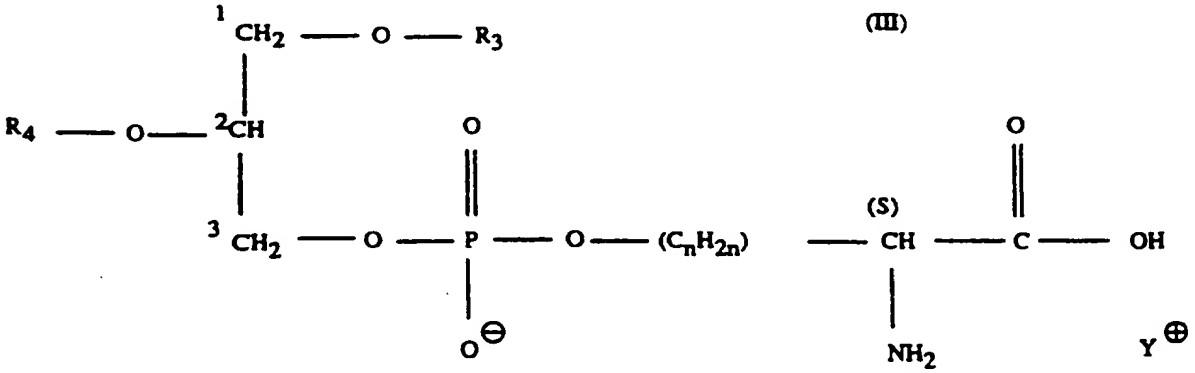
R_2 as C_{10}-C_{20} alkenoyl having an even number of carbon atoms is preferably 9-cis-dodecenoyl, 9-cis-tetradecenoyl, 9-cis-hexadecenoyl, 6-cis-octadecenoyl, 6-trans-octadecenoyl, 9-cis-octadecenoyl, 9-trans-octadecenoyl, 11-cis-octadecenoyl or 9-cis-eicosenoyl. In a phospholipid of formula II, R_a, R_b and R_c are preferably C_1-C_4 alkyl, especially methyl.

In formula II, n is an integer from two to four, preferably two. The group of the formula $-(C_n-H_{2n})-$ is unbranched or branched alkylene, for example 1, 1-ethylene, 1,1-, 1,2- or 1,3-propylene or 1,2-, 1,3- or 1,4-butylene. 1,2-ethylene (n=2) is preferred.

In an especially preferred phospholipid of formula II, R_1 is n-dodecanoyl, n-tetradecanoyl, n-hexadecanoyl or n-octadecanoyl and R_2 is 9-cis-dodecenoyl, 9-cis-tetradecenoyl, 9-cis-hexadecenoyl, 9-cis-octadecenoyl or 9-cis-icosenoyl, R_a, R_b and R_c are methyl and n is two.

A very especially preferred phospholipid of formula II is synthetic 1-n-hexadecanoyl-2-(9-cis-octadecenoyl)-3-sn-phosphatidyl choline.

In certain especially preferred liposomes the lipid component comprises a phospholipid of formula II combined with a synthetic, substantially pure phospholipid of formula



(III)

wherein R_3 and R_4 are each independently of the other C_{10}-C_{20} alkenoyl having an even number f carbon atoms, n is an integer from one to three and $Y^{\oplus}$ is the cation of a

pharmaceutically acceptable base.

In a phospholipid of formula III, R_3 and R_4 as C_{10}-C_{20} alkenoyl having an even number of carbon atoms are preferably 9-cis-dodecenoyl, 9-cis-tetradecenoyl, 9-cis-hexadecenoyl, 6-cis-octadecenoyl, 6-trans-octadecenoyl, 9-cis-octadecenoyl, 9-trans-octadecenoyl, 11-cis-octadecenoyl or 9-cis-eicosenoyl.

The cation $Y^{\oplus}$ of a pharmaceutically acceptable base is, for example, an alkali metal ion, for example the lithium, sodium or potassium ion, the ammonium ion, a mono-, di- or tri-C_1-C_4 alkylammonium ion, for example the trimethyl-, ethyl-, diethyl- or triethyl-ammonium ion, the tetramethylammonium ion, a 2-hydroxyethyl-tri-C_1-C_4 alkyl-ammonium ion, for example the choline cation, or the 2-hydroxyethylammonium ion, or the cation of a basic amino acid, for example lysine or arginine. $Y^{\oplus}$ is preferably the sodium ion.

In an especially preferred phospholipid of formula III, R_3 and R_4 are identical and are, for example, 9-cis-dodecenoyl, 9-cis-tetradecenoyl, 9-cis-hexadecenoyl, 9-cis-octadecenoyl or 9-cis-eicosenoyl, n is one and $Y^{\oplus}$ is the sodium ion.

A very especially preferred phospholipid of formula III is synthetic sodium 1,2-di(9-cis-octadecenoyl)-3-sn-phosphatidyl S-serine.

In another preferred embodiment, the lipid component of the liposomes comprises a di(C_{10}-C_{20} alkanoyl) phosphatidylcholine together with a di(C_{10}-C_{20} alkanoyl) phosphatidylglycerol, the alkanoyl groups having an even number of carbon atoms and the preferred weight ratios being as hereinbefore described. In each phospholipid the two alkanoyl groups may be the same or different and are preferably n-dodecanoyl (lauroyl), n-tetradecanoyl (myristoyl), n-hexadecanoyl (palmitoyl), n-octadecanoyl (stearoyl) or n-eicosanoyl. In an especially preferred embodiment, the di(C_{10}-C_{20} alkanoyl) phosphatidylcholine is distearoyl phosphatidylcholine and the di(C_{10}-C_{20} alkanoyl) phosphatidylglycerol is dipalmitoyl phosphatidylglycerol.

The lipid component of the liposomes may contain cholesterol in addition to the phospholipid(s), the amount of cholesterol being, for example, from 20 to 60, preferably 30 to 50, mol % of the t tal lipid c ntent. In another preferred embodiment, the lipid component of the liposomes comprises a synthetic phosphatidylcholine such as

hereinbefore described, a synthetic phosphatidylserine or phosphatidylglycerol such as hereinbefore described and cholesterol, the preferred weight ratio of phosphatidylcholine to phosphatidylserine or phosphatidylglycerol being as hereinbefore described and the preferred weight ratio of cholesterol to the total phospholipid content being from 1:1 to 1: 5. In an especially preferred embodiment, the lipid component comprises dimyristoyl phosphotidyl choline, cholesterol and dioleoyl phosphatidyl serine.

It is generally desirable to have as high a weight ratio of active compound to lipid as possible consistent with liposome stability. The maximum for this weight ratio may vary depending on the nature and composition of the lipid component, but in general is likely to be about 1:20. However, it has been found that good results can be obtained with liposomes in which this ratio is from 1:100 to 1:50.

The active compound-containing liposomes of the invention can be prepared using known methods for the production of drug-containing liposomes. For example, in one method a solution of the compound of formula I and one or more lipids in an organic solvent, such as an alcohol, ether or halohydrocarbon or mixture thereof, is added gradually, preferably dropwise, to a stirred aqueous medium such as phosphate buffered saline to give an aqueous suspension of liposomes. In another method, one or more lipids and the compound of formula I are dissolved in an organic solvent, such as an alcohol, ether or halohydrocarbon or mixture thereof, the solvent is removed from the resulting solution, for example by freeze drying or by rotary evaporation, and the residue is dispersed in an aqueous medium, such as phosphate buffered saline or an aqueous solution of a sugar, e.g. lactose, to give an aqueous suspension of liposomes.

The aqueous liposome suspension can be treated by known methods to remove the solvent and reduce the size of the liposomes. For example, an aqueous liposome suspension prepared by the first method described above using a water-miscible organic solvent can be subjected to dialysis, optionally after further dilution with an aqueous medium, and the dialysed suspension concentrated by ultrafiltration. An aqueous liposome suspension prepared by the first method, but using a water-immiscible organic solvent, can be evaporated to remove the solvent and then concentrated by ultrafiltration. An aqueous liposome suspension prepared by the second method described above, which usually results in the formation of multilamellar vesicles (MLV's), may be treated to reduce the lipsome size by extruding it through one or more membranes, e.g. polycarbonate membran s, having a selected pore size. Liposomes for use according to the invention

preferably have a particle size below 1 μm, more preferably 20-200 nm, especially 50-100 nm.

The liposomes containing a compound of formula I may be dehydrated, preferably by lyophilisation (freeze drying), to give a dry powder for administration by a dry powder inhaler in the treatment of asthma. The dehydrated liposomes become rehydrated by fluid in the airways of a patient. Lyophilisation of the liposomes is generally carried out in the presence of a cryoprotectant, which may have been incorporated into the aqueous medium used in formation of the liposomes. The cryoprotectant is preferably a sugar, for example a monosaccharide such as glucose, a polymeric sugar such as dextran or, preferably, a disaccharide such as sucrose, lactose, maltose or trehalose. Especially preferred cryoprotectants are lactose and trehalose. In accordance with conventional freeze drying technology, primary lyophilisation is preferably carried out at a temperature below the phase transition temperature of the material to be lyophilised.

Dehydration of the liposomes in the presence of the cryoprotectant results in the formation of a dry powder comprising a mixture of dehydrated liposomes and the cryoprotectant. Where, as is preferred, the cryoprotectant is present in the aqueous medium in which the liposomes are formed, the cryoprotectant is on both the inner and outer surfaces of the liposome particles. The weight ratio of cryoprotectant to the lipid of the liposomes is generally from 1:1 to 4:1, although lower and higher ratios can be used if desired.

If necessary, the product obtained on dehydration of the liposomes containing the compound of formula I, particularly where dehydration has been carried out by lyophilisation in the presence of a cryoprotectant, is ground to give a particle size suitable for use in inhalation therapy, being administered, for example, using a dry powder inhaler device. A suitable size is generally less than 10 μm, preferably 1 to 7 μm. The liposomes containing the compound of formula I may also be used in inhalation therapy in the form of a suspension in an aqueous medium, if necessary after treatment as hereinbefore described to reduce the particle size of the liposomes to an appropriate extent. For use in this form, the liposomes may be prepared in the aqueous medium to be used as a vehicle in inhalation therapy or they may be prepared in another medium and separated therefrom and, optionally, dehydrated as hereinbefore described before incorporation in the aqueous medium to be used as a vehicle in inhalation therapy. The aqueous medium may be an aqueous medium such as is used conventionally as a vehicle in inhalation therapy; it is usually water containing dissolved therein one or more pharmaceutically acceptable

excipients such as sodium chloride, buffering agents, antioxidants and surfactants. A convenient aqueous medium is phosphate-buffered saline, which may contain an antioxidant such as α-tocopherol. When used in inhalation therapy, an aqueous liposome suspension of the invention may be administered by a known nebuliser, for example a pneumatic nebuliser.

A dry powder of the invention, containing the compound of formula I entrapped in dehydrated liposomes, may be placed in capsules, e.g. of gelatin or plastic, or blisters for use in a dry powder inhalation device. The capsules or blisters preferably contain dosage units of the dry powder, which may comprise, for example, 10 to 1000 μg, preferably 50 to 400 μg, of the compound of formula I together with sufficient carrier to give 4 to 40 mg, preferably 20 to 30mg, of dry powder. Alternatively, the dry powder may be placed in the reservoir of a multidose dry powder inhalation device adapted to deliver, for example, 2mg of dry powder per actuation.

The present invention provides, in a further aspect, a method of treating asthma which comprises administration by inhalation of an effective amount of a compound of formula I as hereinbefore defined contained in liposomes or dehydrated liposomes as hereinbefore described.

The daily dosage of the compound of formula I may vary according to the age and weight of the patient to be treated and the severity of the condition. Generally, daily doses may be in the range 50 to 2000 μg, more usually 100 to 1000 μg.

The invention is illustrated by the following Examples, in which parts are by weight unless otherwise stated.

Example 1

1-n-Hexadecanoyl-2-(9-cis-octadecenoyl)-3-sn-phosphatidyl choline (700mg) and sodium 1,2-di(9-cis-octadecenoyl)-3-sn-phosphatidyl S-serine (300mg) are dissolved in tert-butanol (20ml) at 40°C. The solution obtained is mixed with a solution formed by dissolving methyl 9 α-chloro-6α-fluoro- 11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carboxylate (Compound I) (10mg) in tert-butanol (5ml) at 40°C and the temperature returned to 40°C. The resulting solution is added dropwise to a well stirred phosphate buffered saline solution (PBS) of

pH 7.4 (200 ml) at room temperature. The aqueous liposome suspension obtained is dialysed against PBS using an AMICON YM 100 membrane under nitrogen, and concentrated to 20 ml. The concentrated aqueous liposome suspension is filtered successively through filters having a pore size of 0.8 μm and 0.2 μm and dispensed into sterile vials (2 ml each vial). The suspension obtained is suitable for administration by nebuliser in the treatment of asthma by inhalation therapy.

Example 2

The preparation procedure of Example 1 is repeated, but using an aqueous solution containing 94.4g per litre of lactose monohydrate and 0.24g per litre of sodium chloride in place of the phosphate buffered saline used in Example 1 for both liposome formation and dialysis, to give a concentrated aqueous liposome suspension.

Example 3

The concentrated aqueous liposome suspension prepared in Example 2 is freeze dried in a Lyovac GT4 lyophiliser. The cake obtained is micronised using a Trost air impact pulveriser to give a dry powder having a median particle size of 6-7 μm which is suitable for administration by a dry powder inhalation device in the treatment of asthma by inhalation therapy.

Example 4

Distearoyl phosphatidyl choline (700 mg), dipalmitoyl phosphatidyl choline (300 mg) and Compound 1 (20 mg) are dissolved in a 2:1 (by volume) mixture of chloroform and methanol (20 ml). The solvent is removed by rotary evaporation. The residue is dispersed in 40ml of an aqueous lactose solution containing 94.4g per litre of lactose monohydrate and 0.24g per litre of sodium chloride to give an aqueous liposome suspension. This suspension is extruded through 2 200nm polycarbonate membranes twice and 2 100nm polycarbonate membranes ten times at 70°C under a head of nitrogen to reduce the particle size of the liposomes. The resulting suspension is lyophilised and micronised as in Example 3 to give a dry powder which is suitable for administration by a dry powder inhalation device in the treatment of asthma by inhalation therapy.

Example 5

Dimyristoyl phosphatidyl choline (678mg), cholesterol (193mg), dioleoyl phosphatidyl serine (81mg) and Compound 1 (20 mg) are dissolved in tert-butanol (20 ml). The tert-butanol is removed from the resulting solution by freeze drying. The residue is dispersed in an aqueous lactose solution as described in Example 4 and the liposome suspension obtained is extruded as described in Example 4, but at 35°C instead of 70°C, to reduce the size of the liposomes to 100nm. The resulting suspension is lyophilised and micronised as in Example 3 to give a dry powder which is suitable for administration by a dry powder inhalation device in the treatment of asthma by inhalation therapy.

Example 6

The effect of liposomes containing entrapped Compound 1 on eosinophil recruitment is tested in a Brown-Norway rat model of allergen - induced eosinophilia as described by Elwood et al, J. Allergy Clin. Immunol 1991, 88, 951-60. Four groups of inbred male rats, weighing 180 to 220g, are studied:

Group 1: The animals are sensitised by an intraperitoneal injection of 0.9% (wt/vol) suspension of ovalbumin (1mg)/$Al(OH)_3$ (100mg) (1ml) followed 21 days later by a single saline aerosol exposure for 15 minutes.

Group 2: The animals are sensitised with ovalbumin as for Group 1, followed 21 days later by exposure to a 1% ovalbumin aerosol for 15 minutes.

Group 3: The animals are sensitised with ovalbumin as for Group 1, followed 19 days later by a transtracheal injection of the liposome suspension (0.5ml) of Example 1 containing 3 µg of Compound 1 under ketamine anaesthesia and 24 hours later by a further such transtracheal injection. 24 hours after the second injection, the animals are exposed to a 1% ovalbumin aerosol for 15 minutes.

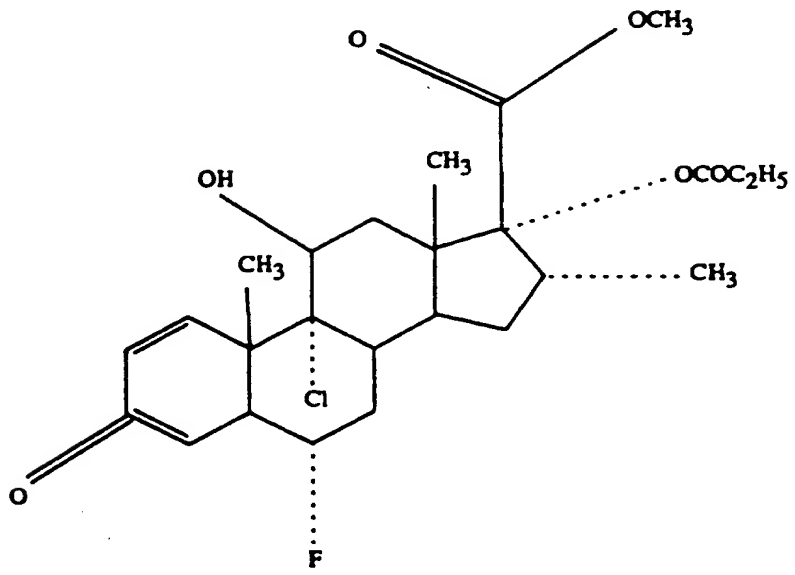
Group 4: The animals are treated as for those of group 3, but using, in place of the liposomes containing Compound 1, placebo liposomes prepared by the same procedure but mitting Compound 1.

For each group of rats, bronchoalveolar lavage is performed 24 hours after the exposure to the aerosol to determine the eosinophil count. The results are as follows:

Group	No. of Eosinophils per rat
1 (saline challenge)	0.25×10^5
2 (ovalbumin challenge)	19.0×10^5
3 (Compound 1 liposomes)	10.3×10^5
4 (placebo liposomes)	16.9×10^5

Claims

1. A pharmaceutical composition comprising, as active ingredient, a compound of formula I



I

contained in liposomes or dehydrated liposomes.

2. A composition according to claim 1, in which the lipid component of the liposomes or dehydrated liposomes comprises at least one synthetic phospholipid.

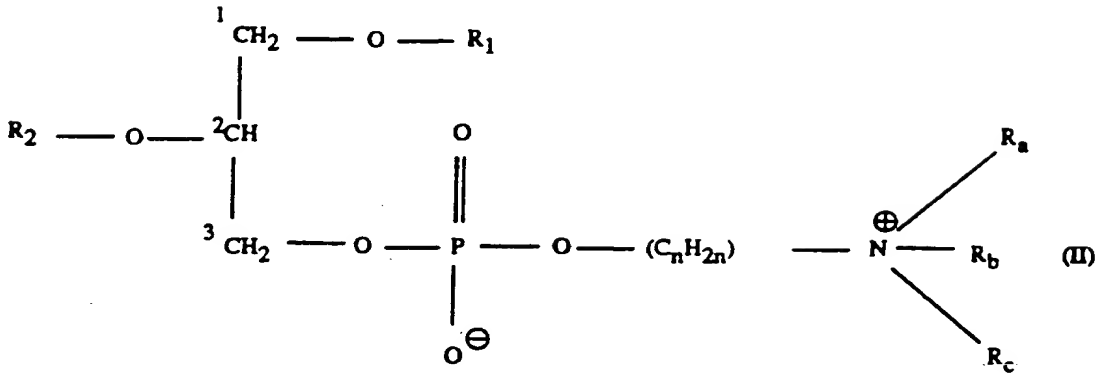
3. A composition according to claim 2, in which the lipid component comprises a synthetic phosphatidyl choline optionally together with a synthetic phosphatidyl serine or synthetic phosphatidyl glycerol.

4. A composition according to claim 3, in which the phosphatidyl serine or phosphatidyl glycerol is present and the weight ratio of the phosphatidyl choline to the phosphatidyl serine or phosphatidyl glycerol is from 60:40 to 95:5.

5. A composition according to claim 4, in which said weight ratio is from 70:30 to 90:10.

6. A composition according to any of claims 3 to 5, in which the lipid component

comprises a synthetic phospholipid of formula II

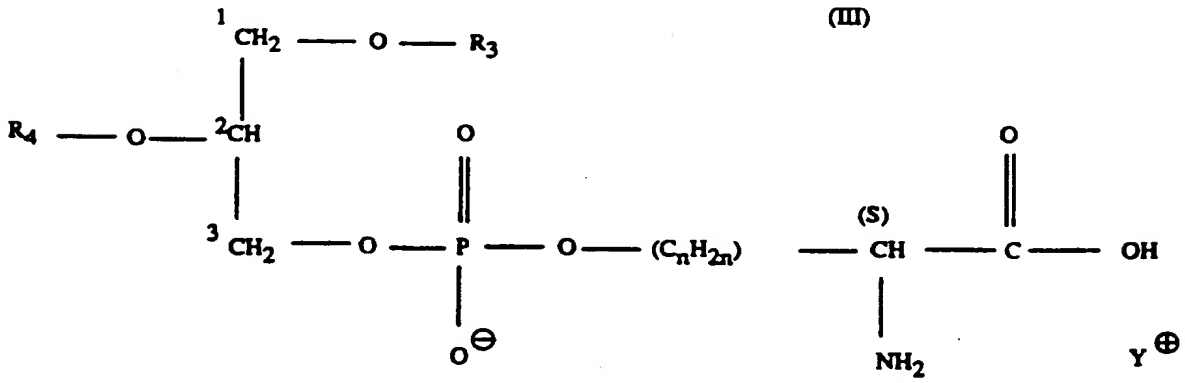


(II)

where R_1 is C_{10}-C_{20} alkanoyl having an even number of carbon atoms, R_2 is C_{10}-C_{20} alkenoyl having an even number of carbon atoms, R_a, R_b and R_c are hydrogen or C_1-C_4 alkyl and n is an integer from two to four.

7. A composition according to claim 6, in which the phospholipid of formula II is 1-n-hexadecanoyl-2-(9-cis-octadecenoyl)-3-sn-phosphatidyl choline.

8. A composition according to any of claims 3 to 7, in which the lipid component comprises a synthetic phospholipid of formula II as defined in claim 6 together with a synthetic phospholipid of formula III



(III)

wherein R_3 and R_4 are each independently of the other C_{10}-C_{20} alkenoyl having an even number f carbon atoms, n is an integer from ne to three and $Y^{\oplus}$ is the cation of a pharmaceutically acceptable base.

9. A composition according to claim 8, in which the phospholipid of formula III is sodium 1, 2-di(9-cis-octadecenoyl)-3-sn-phosphatidyl S-serine.

10. A composition according to any of claims 3 to 5, in which the lipid component comprises a di(C_{10}-C_{20} alkanoyl) phosphatidyl choline with a di(C_{10}-C_{20} alkanoyl) phosphatidyl glycerol.

11. A composition according to claim 10, in which the phosphatidyl choline is distearoyl phosphatidyl choline and the phosphatidyl glycerol is dipalmitoyl phosphatidyl glycerol.

12. A composition according to any of claims 2 to 11, in which the lipid component also contains cholesterol.

13. A composition according to claim 12, in which the amount of cholesterol is from 20 to 60 mol% by weight of the total lipid content.

14. A composition according to claim 12 or 13, in which the lipid component comprises dimyristoyl phosphatidyl choline, cholesterol and dioleoyl phosphatidyl serine.

15. A composition according to any of claims 1 to 14, in which the weight ratio of the compound of formula I to lipid is from 1:100 to 1:50.

16. A composition according to any of claims 1 to 15, in which the liposomes have a particle size below 1 μm.

17. A composition according to any of claims 1 to 16, in which the liposomes are in aqueous suspension.

18. A composition according to any of claims 1 to 16, in the form of a dry powder comprising a mixture of (a) dehydrated liposomes containing a compound of formula I and (b) a cryoprotectant.

19. A composition according to claim 18, in which the weight ratio f cryoprotectant to lipid of the liposomes is from 1:1 to 4:1.

20. A method of preparing a composition according to any of claims 1 to 17 which comprises adding a solution of the compound of formula I and one or more lipids in an organic solvent gradually to a stirred aqueous medium to give an aqueous suspension of liposomes.

21. A method of preparing a composition according to any of claims 1 to 17 which comprises removing the solvent from a solution of one or more lipids and the compound of formula I in an organic solvent and dispersing the residue in an aqueous medium to give an aqueous suspension of liposomes.

22. A method of preparing a composition according to any of claims 1, 18 and 19, which comprises dehydrating liposomes containing a compound of formula I to give a dry powder.

23. A method according to claim 22, in which dehydration is carried out by lyophilisation.

24. A method of treating asthma which comprises administration by inhalation of an effective amount of a compound of formula I as defined in claim 1 contained in liposomes or dehydrated liposomes to a patient in need of said treatment.

25. Use of a composition according to any of claims 1 to 19 in the preparation of a medicament for the treatment of asthma.

26. A composition according to claim 1, substantially as described in any of the Examples.

27. A method according to claim 20, substantially as described in Example 1 or 2.

28. A method according to claim 21, substantially as described in Example 4 or 5.

29. A method according to claim 22, substantially as described in Example 3.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 96/00083

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/127

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 135 476 (CIBA GEIGY AG) 27 March 1985 see page 1 - page 2 see page 18, paragraph 4 - page 19, paragraph 1	1-29
Y	US,A,5 043 165 (RAMACHANDRAN RADHAKRISHNAN) 27 August 1991 see column 5, line 62 - column 8, line 60 see column 16, line 1 - line 41	1-29
Y	EP,A,0 260 241 (AKTIEBOLAGET DRACO) 16 March 1988 see page 3, line 20 - page 4, line 16	1-29
Y	US,A,5 192 528 (RAMACHANDRAN RADHAKRISHNAN ET AL.) 9 March 1993 see column 3, line 15 - column 6, line 8	1-29

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
3 May 1996	21.06.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Tzschoppe, D

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/GB 96/00083

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